Supplementary Appendix

Argentina Population Assumptions

The estimated population of Argentina aged 35-84 years in the year 2010, by age and sex, were obtained from the Argentina National Statistics and Census Institute (Instituto Nacional Estadística y Census, INDEC, http://www.indec.gov.ar). Numbers of 35 year olds entering the model from 2011-2020 were also based on INDEC estimates.

Argentina Mortality Assumptions

Cause-specific mortality data by year, age, and sex were obtained from the Health Vital Statistics (Dirección de Estadísticas e Información en Salud – DEIS-, Minsitry of Health) for the years 1997-2009. The CHD Policy Model-Argentina defined CHD as myocardial infarction (ICD-10 I21, I22), angina and other CHD (ICD-10 I20, I23-I25), and a fixed proportion of ill-defined cardiovascular disease coded events and deaths , named "garbage codes" (ICD-10 I461, I469, I472, I490, I460, I500, I501, I509, I514, I515, I516, I519 and I709). Misclassification of CHD deaths into ill-defined cardiovascular disease codes occurs in many nations, resulting in gross underestimation of CHD mortality, especially in nations that have traditionally coded a large proportion of deaths into these codes. Lozano et al. developed regression equations using standard CHD death rates and the relative risk of CHD attributable to national smoking prevalence to develop correction factors for the ill-defined cardiovascular code use in high- and low-miscoding nations.[1] Because Argentina codes between 10-

11% of all deaths into these ill-defined codes (above the international median of 5%), we re-classified the proportion of ill-defined cardiovascular disease coded deaths recommended for "high ill-defined cardiovascular disease coding" nations. Applying this method to Argentina's CHD mortality data led to an age-standardized increase in annual CHD deaths of approximately 40% in excess of the rate estimated using CHD-specific codes (though estimated deaths in the 65-74 year old category increased by as much as 83%. Stroke deaths were defined using ICD-10 codes I60-I69.

Argentina Cardiovascular Disease Incidence, Case-fatality, and Prevalence

Argentina-specific model inputs for CHD and total stroke incidence, case-fatality, and prevalence were obtained for the CHD Policy Model-Argentina whenever possible (Table 1). Incidence of acute myocardial infarction (AMI) was obtained from a population-based MI registry in a Buenos Aires district[2] and incidence of total stroke from national vital statistics and a hospital admission database maintained by the Ministry of Health of Argentina. Incident cases of stable angina without MI were assumed to be non-fatal, and cases of incident out-of-hospital ischemic cardiac arrest (with or without AMI) were assumed to be universally fatal. In-hospital case-fatality was obtained from an Argentine national hospital survey[3] and the Ministry of Health admissions database, and overall AMI case-fatality (including both out-of-hospital ischemic cardiac arrest and in-hospital CHD deaths) was estimated using the Policy Model after first entering incident CHD, hospitalized AMI case-fatality, and mortality assumptions.

Stroke in-hospital case-fatality was obtained from an Argentine national registry[4] and administrative data, and 28-day case-fatality rates were obtained from population-based Chilean stroke registry, the *Proyecto Investigación de Stroke en Chile: Iquique Stroke Study* (PISCIS, 2000-2002).[5]

Argentina Cardiovascular Risk Factors

Age and sex-specific means of systolic blood pressure, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and body mass index (BMI) were obtained Argentina portion of the Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) Study, a stratified random sample of men and women aged 25-64 years in the city of Buenos Aires during 2003-2004. Anthropometric and laboratory testing were performed at health care institutions using standard risk factor measurement protocols.[6] Estimates of self-reported active and passive smoking prevalence were obtained from the 2009 Argentine National Risk Factor Survey (Segunda Encuesta Nacional de Factores de Riesgo, ENFR) using a tobacco questionnaire adapted from World Health Organization and Pan American Health Organization instruments and validated for Argentina.[7] The CHD Policy Model population is defined as ages 35-84 years, so CARMELA data for ages 35-64 years were used, and estimates for ages 65-84 were imputed based on risk factor age trends observed in the U.S. NHANES. The Policy Model software includes a function that ensures that the age-trend in risk factor levels is preserved as cohorts age upward and new waves of 35 year olds enter with each successive year of the

model simulation. Transfers from one risk factor level to another are included to ensure that the CARMELA or ENFR proportions of the population with each risk factor level are maintained.

Cardiovascular disease event prediction

For the simulations of Argentina, multivariate risk equations were estimated from United States Framingham Heart Study data[8] with CHD (stable or unstable angina, nonfatal myocardial infarction, fatal myocardial infarction, or arrest) or stroke events (ischemic stroke, including transient ischemic attack, plus hemorrhagic stroke)[9] as the outcome. Risk coefficients for age, sex, systolic BP, smoking status, LDL, HDL, diabetes, and BMI were estimated and statistically significant ($P<0.05$) age*risk factor interactions were incorporated into age-specific coefficients for CHD. The prediction model for total stroke includes only age, sex, systolic BP, smoking status, and diabetes.[9] Risk factor beta coefficients were determined for a 60-year-old, the average age of the first onset of CHD or stroke in individuals in examinations 9 to 13, 24, and 25 from the original Framingham Heart Study cohort and 1-6 from the Framingham offspring cohort, for whom adequate data were available for a time-dependent logistic regression analysis. In order to model competing mortality risk, a separate non-CHD death equation was also estimated from Framingham data and includes age, sex, systolic BP, diabetes, and smoking status.

Based on an analysis of Framingham Heart Study data, no independent effect of body mass index was assumed, but rather elevated BMI was assumed to exert its effect on disease risk via changes in associated risk factors.

Specifically, the effect of a one kg/m² increase in BMI was: SBP (males: 1.36 mm Hg, females: 1.40 mm Hg),[10] LDL [males: 0.07 mmol (2.76 mg/dl), females: 0.6 mmol (2.24mg/dl)],[11] and HDL cholesterol [males: 0.4 mmol/l (1.55 mg/dl),[11] females 0.02 mmol/l (0.77 mg/dl)] and risk of diabetes (2.1% M, 1.9%F).[12-13]

CHD states

For the population with CHD, the natural history of CHD was modeled as annual probabilities of transition to new non-fatal CHD states (among combinations of myocardial infarction, cardiac arrest, and receipt of revascularization procedures) were based on data from international studies.

Model Calibration

The CHD Policy Model-Argentina predicted deaths were compared with CHD deaths observed from Argentina vital statistics for the years 1997-2009 (Figure 1). Vital statistic reporting estimated that crude rates of CHD deaths declined between 1999 and 2004 despite the fact that the population aged 65-84 increased by 10%. Ill-defined coded CHD deaths recorded by DEIS remained a constant proportion of total deaths, suggesting that coding practices remained unchanged over that interval. Because of the change in CHD mortality 2000-2004, the model's incidence rates were adjusted to reproduce the total number of deaths reported by the DEIS for 2005 and maintain constant projected age-specific CHD death rates over the years 2005-2040 under fixed case-fatality and risk factor conditions.

Attributable Risk Analysis

Annual risk for CHD is calculated for each model cell by a multivariate logistic regression equation. Therefore annual risk for events is determined by the age, sex, and risk factor relative levels assigned to that cell, and the combined multiplicative effect of the risk factor coefficients. The overall proportion of CHD events explained by the selected major risk factors was obtained by simultaneously setting all of the risk factors to the minimum risk exposure level for the entirety of the 10-year simulation and comparing with a base case in which risk factor levels stayed constant at year 2010 levels. The resulting attributable proportions reflect a hypothetical scenario in which all risk factor exposures are removed at the same time, rather than removing the effect of single risk factors once at a time.[14] Risk for events in each model cell are predicted by a logistic function

Formula 1:

Rate of CHD or stroke in cell = $\exp(\alpha + \beta_{RF}*mean_{RF})/[1+\exp(\alpha + \beta_{RF}*mean_{RF})]$

where α = age-specific rate of disease in the overall population (intercept), β_{RF} = age-specific risk coefficient for a risk factor, and meanRF = age-specific risk factor mean. Thus, in this method the effect of combined and simultaneous risk factor reductions is multiplicative of the relative risks, after adjusting for correlation between risk factors. The multiple risk factor attributable proportion is constrained in a logistic model approach because percent of risk for events "explained" can approach but not exceed 100%.[14]

The proportion of CHD and stroke events attributable to SBP, LDL cholesterol, HDL cholesterol, active smoking, passive smoking, and diabetes were estimated for the base case simulation for the years 2010-2030. Events attributable to

elevated BMI were simulated and reported separately because of the assumption that BMI effects are mediated exclusively through downstream risk factors whose direct effects were already quantified in the main analysis. A baseline with risk factors at 2010 levels was compared with a simulation in which all risk factors were simultaneously set at optimal exposure levels[15] (zero smoking and diabetes exposures and levels of BMI,[16] cholesterol,[17] and blood pressure[18] with lowest risk for events found in large epidemiologic studies, **Figure 1**).

Contributorship statement: JK undertook the literature review, designed of the study, modeled the data, interpreted the results and drafted of the paper. DF undertook the literature review, designed of the study, modeled the data and drafted the paper. RM designed the study and drafted the paper. PC modeled the data and drafted the paper. AM designed the study and drafted the paper. LG designed the study and drafted the paper. EPS designed the study and drafted the paper.

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Data sharing statement: Additional data may be sent upon request

Appendix Table 1: Model inputs for the CHD Policy Model-Argentina

Variable	Source
Population of Argentina & incoming 35 year olds, 2010-2050*	Census; www.indec.gov.ar
Incidence	
CHD	Incidence of hospitalized AMI: Caccavo et al., 2007[2]
Total stroke	Incidence of stroke: national vital statistics and hospital admission registry, Ministry of Health, Argentina (personal communication, Dr. Daniel Ferrante)
Prevalence of CHD in 2010	Non-communicable diseases telephone surveillance system, Ministry of Health
Total and Cause-Specific Mortality	
Total	National vital statistics, www.indec.gov.ar, all deaths in adults age 35-84 years
CHD	1997-2009 vital statistics; using CHD ICD-10 codes I20-25 and 2000 Global Burden of Disease 'garbage code' definitions for a proportion of CHD deaths (see text)
Stroke	1997-2009 vital statistics; using stroke ICD-10 codes I60-69
CHD risk factor means and joint distributions, 2010	Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) Study[6] and Segunda Encuesta Nacional de Factores de Riesgo (Second Argentine National Risk Factor Survey)[7]
Risk factor hazards for CHD and stroke	Framingham Heart Study (U.S.A.) [8-9]
One-day and 28-day CHD case-fatality	
CHD	
In-hospital	Blanco P et al. Encuesta de SAC, 2007[3]
Stroke	
In-hospital	Argentinian National Stroke Registry (ReNACer)[4]

28-day case fatality	Proyecto investigacion de Stroke en Chile: Iquique Stroke Study (PISCIS)[5]

Appendix Table 2: Relative risks for CHD and stroke estimated from cohort studies: the Framingham Heart Study from the United States (1948-present).

*Diabetes defined as having a diagnosis of diabetes, or taking medications for diabetes, or having a fasting glucose ≥ 7.0 mmol.l (≥ 126 mg/dl) For the

Risk factor	Age (5 years)	Systolic BP (20 mm Hg)	LDL Cholesterol (40 mg/dl, 1.03 mmol/l)	HDL Cholesterol (40 mg/dl, 1.03 mmol/l)	Diabetes* (yes/no)	Current smoking (yes/no)¶
Men						
CHD						
Framingham Heart Study Main estimate (95% CI)	1.30 (1.25,1,35)	1.58 (1.45,1.73)	1.44 (1.35,1.55)	0.53 (0.39,0.70)	2.77 (2.61,2.95)	1.44 (1.25,1.66)
Based on INTERHEART Latin America odds ratio for acute myocardial infarction						1.48
Total Stroke†						
Framingham Heart Study RR weighted to reflect higher proportion hemorrhagic stroke in Argentina§	1.33 (1.23,1.45)	1.58 (1.48, 1.70) 2.01	--------	--------	1.40 (1.09,1.81)	1.95 (1.66,2.29)
Women						
CHD						
Framingham Heart Study Main estimate (95% CI)	1.30 (1.25,1,35)	1.90 (1.74, 2.07)	1.44 (1.35,1.55)	0.53 (0.39,0.70)	2.77 (2.61,2.95)	1.62 (1.43,1.83)
INTERHEART odds ratios						1.48
Total Stroke						
Framingham Heart Study RR weighted to reflect higher proportion hemorrhagic stroke in Argentina	1.33 (1.23,1.45)	1.48 (1.38,1.59) 2.01	--------	--------	1.72 (1.34,2.22)	1.80 (1.57, 2.07)

Framingham Heart Study, diabetes was defined similarly except that a cutoff of a fasting glucose ≥ 140mg/dl was used.
¶Actual coefficients used in the model are based on number of cigarettes smoked daily in active smokers: the relative risk reported here was calculated as exp^(cigarettes per day*beta)
†"Total stroke' in the Framingham Heart Study included transient ischemic attack (TIA, ICD-9 435) which did not include TIA. There were too few stroke events in Framingham to allow for estimation of separate ischemic and hemorrhagic stroke multivariate risk functions. 95% confidence intervals were not reported for the published estimates,[9] so standard errors estimated from original Framingham data were used to generate 95% confidence intervals.
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Appendix Table 3: Proportion (%) of incident CHD events allocated to myocardial infarction assumed for non-smokers and active smokers, the CHD Policy Model. The remaining proportion of CHD events are allocated to either angina (stable or unstable) or ischemic cardiac arrest. Overall proportion allocated to myocardial infarction based on U.S. National Hospital Discharge Survey data after adjusting for miscoding and double counting.[19-20]

	Non-smokers		Active Smokers	
Age category	Men	Women	Men	Women
35-44 years	10.2	8.4	69.9	73.6
45-54 years	16.3	15.8	74.6	80.8
55-64 years	26.3	19.7	72.8	75.9
65-74 years	47.0	47.4	72.0	76.7
75-84 years	60.0	63.0	75.6	71.3

Appendix Table 4: Number of cigarettes smoked per day in active smokers, United States (National Health and Nutrition Examination Surveys, 1999-2004) and Argentina (National Risk Factor Survey, 2009),[7] all obtained by self-report.

Cigarettes smoked per day in active smokers	Argentina		United States	
	Men	Women	Men	Women
Age category				
35-44 years	14.6	9.3	11.6	14.9
45-54 years	14.8	11.8	22.1	17.0
55-64 years	14.7	11.5	21.0	18.0
65-74 years	14.0	10.3	9.9	14.0
75-84 years	8.3	4.5	7.2	6.1

Appendix Table 5: Prevalence of diabetes, cholesterol, hypertension, obesity and smoking by age groups and sex, in Argentina (National Risk Factor Survey, 2009),[7] all obtained by self-report

		diabetes		cholesterol		hypertension		obesity			smoking		
		no	yes	no	yes	no	yes	normal	overweight	obese	non smokers	exposed SHS	Smokers
35-44 years	men	95,2%	4,8%	73,1%	26,9%	74,7%	25,3%	32,2%	45,3%	22,5%	40,4%	24,1%	35,5%
	women	90,8%	9,2%	85,3%	17,5%	71,8%	28,2%	52,9%	28,2%	18,8%	49,6%	26,8%	23,6%
45-54 years	men	89,4%	10,6%	71,9%	34,7%	63,9%	36,1%	23,2%	49,1%	27,6%	39,6%	24,4%	36,0%
	women	89,1%	10,9%	81,9%	29,6%	62,7%	37,3%	45,8%	31,0%	23,1%	44,1%	24,0%	32,0%
55-64 years	men	82,8%	17,2%	65,2%	41,2%	48,6%	51,4%	25,5%	47,2%	27,2%	45,8%	24,2%	30,0%
	women	84,1%	15,9%	70,4%	42,0%	50,1%	49,9%	39,3%	34,1%	26,6%	55,2%	24,7%	20,1%
65-74 years	men	79,1%	20,9%	58,7%	37,8%	40,3%	59,7%	27,4%	47,5%	24,9%	60,7%	19,9%	19,4%
	women	82,5%	17,5%	58,0%	44,7%	36,3%	63,7%	38,2%	38,6%	23,2%	64,1%	26,6%	9,3%
75-84 years	men	79,5%	20,5%	62,2%	32,2%	37,8%	62,2%	35,9%	48,6%	15,4%	76,4%	16,1%	7,4%
	women	82,1%	17,9%	55,3%	42,9%	33,6%	66,4%	45,7%	40,1%	14,2%	73,9%	22,0%	4,1%

Supplementary Appendix References

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